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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
BELYAVSKYI, MICHAIL A

ART UNIT	PAPER NUMBER
1644	12

DATE MAILED: 09/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/818,247	MOSTOV ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,10-13 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continuation of Disposition of Claims: Claims pending in the application are 1-7,10-13,15-20,23,24,26-36,39,41-48,50,51,53-70,73,75-84, 87 and 89-93.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 16-20,23,24,26-36,39,41-48,50,51,53-70,73,75-84,87 and 89-93.

DETAILED ACTION

1. Applicant's amendment, filed 06/30/03 (Paper No. 11), is acknowledged.

Claims 1-7, 10-13, 15-20, 23, 24,26-36, 39, 41-48, 50, 51, 53-70, 73, 75-84, 87, 89 and 90-93 are pending.

2. Applicant's election with traverse of Group I, claims 1-10 (now claims 1-7 and 10) in Paper No. 11 is acknowledged.
Applicant traverse the Restriction Requirement on the grounds that the inventions must be both independent and distinct and an undue search burden on the examiner. However, MPEP 803 states that the Inventions be either independent or distinct and a burden on the Examiner if restriction is required.

Regarding applicant's comments about undue burden, the MPEP 803 (August 2001) states that "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification separate status in the art, or a different field of search". The Restriction Requirement enunciated in the previous Office Action meets this criteria, indicates that inventions recognized divergent subject matter and that a different field of search would be required based upon the structurally distinct products recited and the various methods of use comprising distinct method steps. Moreover, a prior art search also requires a literature search. All the above establishes that serious burden is placed on the examiner by the examination of more than one Group. The Inventions are distinct for reasons elaborated in the previous Office Action and above.

The requirement is still deemed proper and is therefore made FINAL.

Upon consideration of applicant's arguments, filed 06/30/03 (Paper No. 11), the prior art search has been extended to include claims 11-15 (now claims 11-13 and 15) of Groups II –XI. The restriction requirement between claims 1-15 (now claims 11-13 and 15) has been withdrawn.

3. Claims 16-20, 23, 24, 26-36, 39, 41-48, 50, 51, 53-70, 73, 75-84, 87, and 89-93 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

Claims 1-7, 10-13 and 15, drawn to a ligand that binds specifically to a region of a pIgR and does not bind to the stalk of said pIgR and further comprising a biological active component under consideration in the instant application.

4. The disclosure is objected to because it contains an embedded hyperlink , for example on page 30, line 21 and page 34, line 28. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-7, 10-13 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite and ambiguous in the recitation of " binds to most abundant form of SC present in the organ" and " does not binds to the stalk under physiological conditions". The characteristics and metes and bounds of " most abundant form of SC present in the organ" and "physiological conditions" are unclear and indefinite.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-4, 10-13 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a antibodies that binds specifically to a B-region of pIgR, and does not bind to secretory component of pIgR and does not bind to the stalk of said pIgR which confers on the conjugate the ability to bind selectively to a target, wherein a conjugate is a chimeric molecule comprised said antibody coupled to a biologically active component, wherein biological active component is a nucleic acid encoding the wildtype cystic fibrosis transmembrane conductance regulator, as recited in claim 13 or as recited in canceled claim 14 and claim 15 does not reasonably provide enablement for *any* ligand that binds to *any* region of

pIgR or *any* ligand comprising a binding component for binding to *any* region of pIgG and *any* biological active component . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

There is insufficient guidance and direction as to how to make *any* ligand that binds to *any* region of pIgR or *any* ligand comprising a binding component for binding to *any* region of pIgG and *any* biological active component . The Specification as filed on page 37, lines 7-15 disclosed that "ligand" can be "all molecules capable of specifically binding to B region of pIgG and that such ligands includes peptides or small organic molecules or nucleic acids. Moreover, Applicant himself acknowledge that it is essential for the invention that antibodies should bind specifically only to B region (not any region) of the pIgR, the region of the SC adjacent to the cleavages site which undergoes further proteolytic digestion or secondary cleavage following from intact pIgR (see page 13, lines 5-30 in particular).
Applicant has not provided sufficient biochemical information (e.g. structural characteristics, amino acid composition , physicochemical properties, etc) that distinctly identifies such "ligands" and "any biological active components" other than antibodies that binds specifically to B region of pIgG encompassed by claims 6-7 and biological active component is a nucleic acid encoding the wildtype cystic fibrosis transmembrane conductance regulator, as recited in claim 13 or as recited in claim 14 and 15 . While any "ligand that binds to a region of pIgG " may have some notion of the activity of the "ligand", claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make such agents, commensurate in scope with the claimed invention. The techniques required to use a ligand which is an antibody differ from those required to use other non-antibody proteins and peptides, nucleic acids in binding assays. For instance, Ferkol et al (IDS) teach that while antibody may be used as the ligand for receptor mediated gene transfer, the natural ligands may be unstable.
Since the instant fact pattern fails to indicate that representative number of structurally related compounds is disclosed, the artisan would not know the identity of a reasonable number of representative compounds falling within the scope of the instant claims and consequently would not know how to make them.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed *any* ligand that binds to *any* region of pIgR or *any* ligand comprising a binding component for binding to *any* region of pIgG and *any* biological active component in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

9. Claims 1-4, 10-13 and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of : a antibodies that binds specifically to a B-region of pIgR, and does not bind to secretory component of pIgR and does not bind to the stalk of said pIgR.

Applicant is not in possession of : *any* ligand that binds to *any* region of pIgR or *any* ligand comprising a binding component for binding to *any* region of pIgG and *any* biological active component .

The claimed invention is drawn to a genuses of "ligands" and "biologically active components", however, structural identifying characteristics of the genuses are not disclosed. There is no evidence that there is any *per se* structure/function relationship between the disclosed antibody that binds specifically to a B-region of pIgR, and does not bind to secretory component of pIgR and does not bind to the stalk of said pIgR. and *any* ligand that binds to *any* region of pIgR or *any* ligand comprising a binding component for binding to *any* region of pIgG and *any* biological active component .

Applicant has disclosed a limited number of species; therefore, the skilled artisan cannot envision all the contemplated possibilities of the *any* ligand that binds to *any* region of pIgR recited in the instant claims. Consequently, conception in either case cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description

requires more than a mere statement that it is part of the invention. The sequences themselves are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).

A description of a genus of ligands may be achieved by means of a recitation of a representative number of ligands, defined by amino acid sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 37(c) of this title before the invention thereof by the applicant for patent.

11. Claims 1-7 and 10 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 6,046,037, as evidenced by the specification disclosure as filed on overlapping pages 38-39 ; Bost et al. (Immunol. Invest. 1988; 17:577-586) and Bendayan (J. Histochem. Cytochem. 1995; 43: 881-886).

US Patent '037 teaches an antibody that can specifically binds to amino acid 450-606 of the aminal pIgR of SEQ ID NO:4. It is noted that said region is highly homologous (97.7 %) to residues 487-603 of the instant SEQ ID, 1, (see attached sequence alignment). US Patent '037 teaches that said antibody is a humanized antibody or consisting of a recombinant single variable region.(see column 20, lines 40-65 in particular).

As is evidenced by the specification disclosure as filed on overlapping pages 38-39 , residues 487-603 of the instant SEQ ID, 1, is corresponding to the B region of pIgR.

Since amino acid 450-606 of the aminal pIgR of SEQ ID NO:4 are 97.7 % homologous to residues 487-603 of the instant SEQ ID, 1, the antibody of the US Patent '037 document will cross-react with the claimed region of a pIgR.

That an antibody "cross-reacts", i.e. binds to more than one protein sequence, does not mean that the antibody does not "specifically react" with both proteins. Evidentiary reference Bost et al. (Immunol. Invest. 1988; 17:577-586) disclose antibodies which "cross-react" with IL-2 and HIV envelope protein, but establish that the binding of each protein is due to the presence of a homologous sequence in each protein in which 4 of 6 residues were identical (see entire document, but especially the Abstract and Discussion). Antibodies which bound either the HIV or IL-2 derived sequence did not cross-react with irrelevant peptides (e.g., Results, page 579). Similarly, Bendayan (J. Histochem. Cytochem. 1995; 43: 881-886) characterizes the specific reactivity of a monoclonal antibody produced to human proinsulin, and shows that although the antibody is highly specific, it is nevertheless able to bind to not only human proinsulin, but to proinsulin from other species and even a distinct protein, glucagons, based upon conservation of an Arg-Arg dipeptide sequence in each of these molecules (see entire document). Bendayan concludes that "an antibody directed against such a sequence, although still yielding specific labeling, could reveal different molecules not related to the original antigen" (page 886, last paragraph). Consequently, it was well known in the art that antibody binding of distinct proteins was indeed specific.

Claims 2, 4 and 10 are included because the claimed functional limitation would be inherent properties of the referenced antibody because of the high homology of the sequences (at the residues indicated supra) would allow for cross-reactivity of the referenced antibody . Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibodies do not have the functional laminations as recited in the claims. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); *In re Fitzgerald et al.*, 205 USPQ 594 (CCPA 1980).

The reference teaching anticipates the claimed invention.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1, 11, 12, 13 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,046,037 as evidenced by the specification disclosure as filed on overlapping pages 38-39 ; Bost et al. (Immunol. Invest. 1988; 17:577-586) and Bendayan (J. Histochem. Cytochem. 1995; 43: 881-886) in view of US Patent 6,440,419 and US Patent 6,340,743

The teaching of US Patent '037 ; the specification disclosure as filed on overlapping pages 38-39 ; Bost et al. (Immunol. Invest. 1988; 17:577-586) and Bendayan (J. Histochem. Cytochem. 1995; 43: 881-886) have been discussed, supra.

US Patent '037 does not teaches an antibody comprising binding component to pIgR and a biological active component wherein biological active component is a nucleic acid encoding the wildtype cystic fibrosis transmembrane conductance regulator, as recited in claim 13 or a small molecule as recited 15.

US Patent '419 teaches a targeting molecules, including antibody, for use in delivering biological active components to (see entire documents, Abstract in particular). US Patent 6,440,419 teaches that biological active components can be therapeutic agents and small molecules (see column 5, lines 5-15 in particular). US Patent 6,440,419 teaches that there is a remains need to improve targeted delivery of biological active components to epithelial cells (see overlapping columns 1-2 in particular).

US Patent '743 teaches that is conventional to target a biological active components to epithelial cells using an antibody that binds specifically to the stalk of a pIgR (see entire document, Claim 1 in particular) . US Patent 6,340,743 teaches antibody comprising binding component to pIgR and a biological active component, wherein the biological active component is a nucleic acid encoding the wildtype cystic fibrosis transmembrane conductance regulator (see claims 11 and 13 in particular). US Patent 6,340,743 teaches that using said antibodies a highly efficient and convenient means to transfer biological active component into epithelial cells (see overlapping columns 1-2 in particular)

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent '419 and US Patent '743 to those of US Patent '037 to obtain a claimed antibody comprising binding component to pIgR and a biological active component wherein the biological active component is a nucleic acid encoding the wild type cystic fibrosis transmembrane conductance regulator.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because there is a remains need to improve targeted delivery of biological active components to epithelial cells , that can be done by using an antibody that binds specifically to the stalk of a pIgR , as taught by US Patent '743 or antibody as taught by US Patent '419. Said antibody can be substituted by antibody taught by US Patent '419.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. No claim is allowed.

15. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is (703) 308-4232. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Michail Belyavskyi, Ph.D.
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September 22, 2003

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